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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,510	05/09/2002	Arthur Kammeijer	2799/66496/RDK	8678

7590 05/05/2005

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,510	KAMMEIJER ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

I. The objection of the specification is maintained for the reasons of record.

II. The rejection of the claim 17 under 35 USC 112, first paragraph, is maintained for the reasons of record.

III. The rejection of the claim 17 under 35 USC 112, second paragraph, is not maintained in light of the amendment.

IV. The rejection of the claim 18 under 35 USC 102(b) as being anticipated by Roberts et al. (US 3515789) is maintained for the reasons of record.

V. The rejection of the claim 17 under 35 USC 102(e) as being anticipated by Hart (Us 6133318) is not maintained in light of the amendment.

VI. The Applicant's amendment necessitates a new ground of rejection(s) in this Office Action.

Status of Application

1. By the Amendment filed December 21, 2004, claims 17 and 18 have been amended; claim 19 has been cancelled; and claims 20-21 have been newly added. Claims 17-18 and 20-21 are currently pending for prosecution on the merits.

Specification

2. The specification is objected to because of the following informalities: Throughout the specification, applicant refers to Table 4 (e.g., page 16, line 20; page 17, lines 1-2, 11, 14 and 19; page 18, lines 1, 3 and 11). However, there is no Table 4 in the specification. It appears that

applicant failed to include it into the original specification. In case applicant files the amendment to correct the deficiency, applicant is advised not to introduce new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

3. The specification is objected to because of the following informalities: The specification recites in page 19, lines 25-26 that four fractions, designated as Rτ 8, Rτ 10, Rτ 14, Rτ 17 are finally selected for identification (peak A, 1-3 in Fig. 4). However, there is insufficient antecedent basis for "Rτ 8, Rτ 10, Rτ 14, Rτ 17" and "peak 1-3" in Figure 4. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing contact hypersensitivity with "imidazole-4-carboxylaldehyde, imidazole-4-acetic acid or imidazole-4-carboxylic acid", does not reasonably provide enablement for a method of modulating an immune response with "a product of oxidation of urocanic acid with a reactive oxygen species or a salt thereof" or "imidazole-4-carboxylaldehyde, imidazole-4-acetic acid or imidazole-4-carboxylic acid". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention relates to a method of modulating an immune response of an animal with a pharmaceutical composition comprising an oxidation product of urocanic acid.

(2) The state of the prior art

There are no known compounds of similar structure which have been demonstrated to modulate all types of immune response.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement

obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

(5) The breadth of the claims

The breadth of the claims encompasses the complex systems of a body's defense reaction against invading substances including a wide range of humoral cell (B-cells) response and cell-mediated immune response (T-cells), wherein said responses are stimulated, inhibited, partially stimulated or partially inhibited by the administration of the claimed compounds.

The broad scope of the instant invention is further exacerbated by the instantly claimed "an oxidation product of urocanic acid". The breadth of the instant "an oxidation product of urocanic acid" encompasses imidazole-4-carboxyaldehyde (ImCHO), imidazole-4-acetic acid (ImAc), imidazole-4-carboxylic acid (ImCOOH), glyoxylic acid, oxalic acid, CO2 and other imidazolic UCA oxidation products (unidentified peaks in HPLC analysis).

(6) The amount of direction or guidance presented or (7) The presence or absence of working examples

The instant specification discloses that the invention provides use of a pharmaceutical composition comprising an oxidation product of urocanic acid for modulating immune responses against various stimuli, thereby mimicking a, previously unknown, natural action of said product (page 4, lines 13-20). The specification also discloses imidazole-4-carboxyaldehyde (ImCHO), imidazole-4-acetic acid (ImAc), imidazole-4-carboxylic acid (ImCOOH), glyoxylic acid and oxalic acid as examples of oxidation product of urocanic acid (UCA). To test the claimed activity of the oxidation product of urocanic acid, the specification discloses the inhibitory effect of the UCA oxidation products in reducing the ear swelling (Fig. 5). The study (Fig. 5) shows that the

imidazoles alone only a moderate effect was observed, however, when tested mixed together, the largest reduction was observed. The study also shows that the glycoxylic acid and oxalic acid did not exhibit significant inhibition of contact hypersensitivity.

As discussed above, the specification fails to show that all of the claimed "oxidation product of urocanic acid" would behave similarly. Clearly, the skill artisan would have expected in reading the instant specification (especially page 19, lines 1-16) that the full scope of "oxidation product of urocanic acid" are not capable of accomplishing the desired result of the claimed invention.

As discussed above, although specification discloses the inhibitory effects of the UCA oxidation products in reducing the ear swelling, however, the skill artisan would have not arrived at the conclusion of the claimed utility in modulating immune response. There is no demonstrated correlation that tests and results apply to the claimed conditions.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of

"oxidation product of urocanic acid" and "modulating immune response" that would enabled in this specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 17, 18, 20 are rejected under 35 U.S.C. 102(b) as being anticiapted by Roberts et al. (US 3515789).

Roberts teaches use of imidazole-4-acetic acid (imidazoleacetic acid) for inducing analgesia in a warm-blooded animal (column 1, lines 15-23; column 2, lines 23-54; claims).

Although the reference is silent about the activity of imidazole-4-acetic acid in modulating an immune response of an animal, such property or characteristic must be inherently

presented in the referenced method. Since the administration of the same compound to the same population group (recipient) would inherently possess the claimed therapeutic utility, therefore, the reference anticipates the claimed invention even absent explicit recitations of the mechanism of action.

6. Claims 17 and 21 are rejected under 35 U.S.C. 102(e) as being anticiapted by Schneider et al. (US 6281244).

Schneider teaches use of composition comprising glycine for treatment of acute or chronic graft rejection by modulating tumor necrosis factor (TNF) levels.

Although Schneider does not specifically mention about the activity of glycine (which is the claimed oxidation product of urocanic acid) in modulating an immune response of an animal, such property or characteristic must be inherently presented in the referenced method. Since the administration of the same compound to the same population group (recipient) would inherently possess the claimed therapeutic utility, therefore, the reference anticipates the claimed invention even absent explicit recitations of the mechanism of action.

Response to Arguments

7. Applicant's arguments filed December 21, 2004 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that "Rτ 8, Rτ 10, Rτ 14, Rτ 17" refers to retention times. Applicant alleges that with the retention time, once can see from Figure 4 which peaks are collected.

This argument is not found persuasive. There is no dispute between the Examiner and the Applicant that "Rτ 8, Rτ 10, Rτ 14, Rτ 17" refers to retention times. However, the applicant's reference to Peak 1-3 in Figure 4 that corresponds to Rτ 10, Rτ 14 and Rτ 17 respectively lacks sufficient antecedent basis in the specification. The peaks in Figure 4 are depicted as A, B, C, D, E, F and G, not Peak 1-3. It is not clear what Peak 1-3 refers to. Applicant is requested to clarify on this issue.

Applicant's argument in the response takes the position that the specification provides ample teaching for the person skilled in the art to identify product of oxidation of urocanic acid with a reactive oxygen species having the desired activity. Thus, the amount of experimentation is not undue, as the specification shows a range of oxidation products having the activity.

This argument is not found persuasive. Although the specification shows other oxidation products than imidazole-4-carboxylaldehyde, imidazole-4-acetic acid, imidazole-4-carboxylic acid, and mixtures thereof, the activity of the other products is not similar as the imidazole-4-carboxylaldehyde, imidazole-4-acetic acid, imidazole-4-carboxylic acid, and mixtures thereof. In fact, glyoxylic acid (which reads on the instantly claimed "a product of oxidation of urocanic acid with a reactive oxygen species or a salt thereof" does not show significant inhibition of contact hypersensitivity. Clearly, not all of the claimed products of urocanic acid with a reactive oxygen species or a salt thereof are enabled in this invention.

As the Applicant also acknowledges in the Argument (bottom of the page 7 of the Remarks/Argument filed December 21, 2004), not all of the claimed oxidation products of UCA have been identified. Without sufficient guidance from the specification in regards to how to

isolate "other unidentified oxidation products of UCA" and test its activity, the skill artisan would not envision which compounds in "other unidentified oxidation products of UCA" are capable of accomplishing the desired activity of the instant invention. As discussed above, the instant specification only shows enabling disclosure for imidazole-4-carboxylaldehyde, imidazole-4-acetic acid, imidazole-4-carboxylic acid and their activity in reducing contact hypersensitivity.

Applicant's argument in the response takes the position that there is no commercial product mentioned by the Examiner, so it cannot be said that the composition was ever administered to a subject population in a dosage or form that modulated an immune response.

This argument is not found persuasive. Unlike Applicant's argument, Roberts discloses the administration of the imidazole-4-acetic acid in various dosage forms (i.e., parenteral, oral), preferably orally, to the warm blood animals (column 1, lines 47-59; column 3, lines 7-12). Therefore, the Examiner maintains that the administration of the same compound to the same population group (recipient) would inherently possess the claimed therapeutic utility, therefore, the reference anticipates the claimed invention even absent explicit recitations of the mechanism of action.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

VICKIE KIM
PRIMARY EXAMINER

Brian Kwon
Patent Examiner
AU 1614